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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,448	ALPHEY, LUKE	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *22,28,31,32 and 36-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-27,29,30 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-42 are pending.

Applicant's election with traverse of group I in the reply filed on 12/1/08 is acknowledged. The traversal is on the ground(s) that that the claimed invention is obvious over this reference, at least in part because Horn does not teach the positive control and reserves the right to traverse when and if a formal rejection is made. Traverse of the requirement for restriction is made, at least in part, on the grounds that the claims are united by the features of the claims of Group I (especially claim 1) and the Examiner is mistaken in the interpretation of the Horn reference. Applicant does not admit that any claims group is an obvious variant of any other claims group. This is not found persuasive because Horn teaches a product of the gene to be expressed and at least serves as a positive transcriptional control factor.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22, 28, 31-32, 36-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/1/08.

Claims 1-21, 23-27, 29-30 and 33-35 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-16, 18-21, 23-24, 29-30, are rejected under 35 U.S.C. 102(b) as being anticipated by **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)].

Heinrich et al teach a tetracycline-repressible female-specific lethal genetic system in the *Drosophila melanogaster* fly. One component of the system is the tetracycline-controlled transactivator gene under the control of the fat body and female-specific transcription enhancer from the yolk protein 1 (yp1) gene. The other component consists of the proapoptotic gene hid under the control of a tetracycline-responsive element. Males and females of a strain carrying both components are viable on medium supplemented with tetracycline, but only males survive on normal medium (abstract) **(claim 1).** Heinrich teaches the expression of tTA is controlled with the female- and fat-body-specific transcription enhancer from the yp1 gene (figure 1) **(claim 2).** Heinrich teaches the yp1 enhancer is upstream of the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 2-4, 20-21, 23**). Heinrich teaches in the absence of tetracycline, tTA binds to tetO and induced expression of the proapoptotic gene hid **(claim 6).** Heinrich teaches the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 7-9, 14).** Heinrich teaches the loss of fat body results in female-specific lethality (figure 1) and because ectopic expression of the proapoptotic gene hid can lead to transactivator (tTA), which is inactive in the presence of tetracycline expression of tTA is controlled with the female specific enhancer from the Drosophila yolk protein 1 (yp1) gene **(claims 10-12).** Heinrich teaches because the components of the system are either conserved (yolk protein genes) or known to function in both Drosophila and mammalian cells, the system could be used to make genetic-sexing strains for a variety of insect pests that can be genetically engineered (p 8229, 2nd column, 1st paragraph) **(claims 13, 16, 18, 20-21, 23).** Heinrich teaches the system was designed such that female flies would die in the absence of tetracycline

because of widespread cell death in the fat body, expression of tTA is controlled by the female- and fat-body-specific enhancer from the yp1 gene, binding of tTA to tetO results in activation of expression of the proapoptotic gene hid and induction of apoptosis in fat body results in female-specific lethality, because the fat body is an important tissue for metabolism and food storage in **insects (claims 14-21, 23-24).** Heinrich teaches the amount of induced ectopic cell death is very sensitive to the level of ectopic *hid* expression, which in the female lethal system depends directly on the level of tTA expression (p 8231, 2nd column, last paragraph) (**claim 18).** Transgene expression is influenced by the local chromatin environment, and tTA expression is controlled by the *yp1* enhancer, which may explain why the efficiency of the system depends on the sites of integration of the constructs and the level of yeast in the diet and the position effects could be minimized by bracketing the *yp1-tTA* and *tetO-hid* constructs with insulator elements **(claims 29, 30).** Heinrich teaches the effect of diet on female lethality is consistent with previous studies that showed that the *yp1* fat body enhancer is responsive to diet, particularly yeast and it will be of interest to determine whether the diet response is mediated via either the sex-specific double-sex protein or the proteins that bind to the b-zip or w3 sites of the enhancer, because the binding sites for all three proteins are required for enhancer function *in vivo* (p 8231, 2nd column, last paragraph) **(claim 19).** Heinrich teaches genes involved in the diet response potentially could be identified by carrying out sensitive genetic screens for mutations that either enhance female lethality on a low-yeast diet or suppress lethality on a high-yeast diet (p 8231, 2nd column, last paragraph).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA

1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. I*n re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972) and In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34(CCPA 1977)).

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Applicant is referred to MPEP 2112 for further discussion on inherency.

Thus, the claimed invention is anticipated by Heinrich et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 18-21, 23-24, 29-30, are rejected under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Savakis et al** (US 2003/0150007); Loukeris et al (PNAS, 92: 9485-9489, 1995).

Heinrich et al teach a tetracycline-repressible female-specific lethal genetic system in the *Drosophila melanogaster* fly. One component of the system is the tetracycline-controlled transactivator gene under the control of the fat body and female-specific transcription enhancer from the yolk protein 1 (yp1) gene. The other component consists of the proapoptotic gene hid under the control of a tetracycline-responsive element. Males and females of a strain carrying both components are viable on medium supplemented with tetracycline, but only males survive on normal medium (abstract) **(claim 1).** Heinrich teaches the expression of tTA is controlled with the female- and fat-body-specific transcription enhancer from the yp1 gene (figure 1) **(claim 2).** Heinrich teaches the yp1 enhancer is upstream of the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 2-4, 20-21, 23**). Heinrich teaches in the absence of tetracycline, tTA binds to tetO and induced expression of the proapoptotic gene hid **(claim 6).** Heinrich teaches the hsp70 minimal promoter that is used to drive expression of the tTA coding sequence (p 8229, 2nd column bridge to p 8223) **(claims 7-9, 14).** Heinrich teaches the loss of fat body results in female-specific lethality (figure 1) and because ectopic expression of the proapoptotic gene hid can lead to transactivator (tTA), which is inactive in the presence of tetracycline expression of tTA is controlled with the female specific enhancer from the Drosophila yolk protein 1 (yp1) gene **(claims 10-12).** Heinrich teaches because the components of the system are either conserved (yolk protein genes) or known to function in both Drosophila and mammalian cells, the system could be used to make genetic-sexing strains for a variety of insect pests that can be genetically

engineered (p 8229, 2nd column, 1st paragraph) **(claims 13, 16, 20-21, 23).** Heinrich teaches the system was designed such that female flies would die in the absence of tetracycline because of widespread cell death in the fat body, expression of tTA is controlled by the female- and fat-body-specific enhancer from the yp1 gene, binding of tTA to tetO results in activation of expression of the proapoptotic gene hid and induction of apoptosis in fat body results in female-specific lethality, because the fat body is an important tissue for metabolism and food storage in **insects (claims 14-21, 23-24). Heinrich teaches t**he amount of induced ectopic cell death is very sensitive to the level of ectopic *hid* expression, which in the female lethal system depends directly on the level of tTA expression (p 8231, 2nd column, last paragraph) (**claim 18).** Transgene expression is influenced by the local chromatin environment, and tTA expression is controlled by the *yp1* enhancer, which may explain why the efficiency of the system depends on the sites of integration of the constructs and the level of yeast in the diet and the position effects could be minimized by bracketing the *yp1-tTA* and *tetO-hid* constructs with insulator elements **(claims 29, 30). Heinrich teaches t**he effect of diet on female lethality is consistent with previous studies that showed that the *yp1* fat body enhancer is responsive to diet, particularly yeast and it will be of interest to determine whether the diet response is mediated via either the sex-specific double-sex protein or the proteins that bind to the b-zip or w3 sites of the enhancer, because the binding sites for all three proteins are required for enhancer function *in vivo* (p 8231, 2nd column, last paragraph) **(claim 19).** Genes involved in the diet response potentially could be identified by carrying out sensitive genetic screens for mutations that either enhance female lethality on a low-yeast diet or suppress lethality on a high-yeast diet (p 8231, 2nd column, last paragraph). Heinrich differs from the present invention for not teaching wherein the gene is modified to at least partially follow codon usage in a species in which the system is for use. Heinrich suggests although said system is effective in *Drosophila*, it is likely that the

system will be applicable to other insects (p 8232, 1st column, 2nd paragraph). The tTA is functional in both *Drosophila* and in mammalian cells and is thus likely to be functional in other insects. Similarly, the *Drosophila hid* gene has been shown to induce apoptosis in mammalian cells. Heinrich also teaches that even though the system works in Drosophila it may also work in insects. Heinrich teaches that it is possible that the *Drosophila yp1* enhancer may not retain the correct tissue and sex specificity in other insects. Indeed, the regulatory regions from the housefly yolk protein genes show the correct tissue specificity but not sex specificity in *Drosophila*, suggesting that it might be necessary to isolate the yolk protein genes from the insect species of interest. Yolk protein genes have been isolated from a number of insect species including the medfly (p 8232, 1st column, 2nd paragraph). The availability of these genes, methods for germline transformation, and the current use of sterile insect control (SIT) to control the medfly make this species attractive for testing the repressible female-lethal genetic system. Heinrich suggests that culture medium will be an important consideration in developing this system in other insects (p 8232, 1st column, 2nd paragraph). Heinrich differs from the present invention for not teaching codon usage in the system.

However at the time of the instant invention **Savakis et al** use of modified transposon wherein the modification includes removal or disruption of transposase sequences or the incorporation of one or more heterologous coding sequences and/or expression controls sequences (see para. 23 of the published application). Although, Savakis et al exemplified type-2 transposon such as Minos to generate transgenic animal, however, he generally embraced the idea of using any transposon (see para 22). It is noted that Savakis et al contemplate heterologous to genetic sequences that are from a species other than the organism or transposon of interest (see para. 24 of the published application). Savakis et al disclose variety of promoters that could be used including tissue-specific promoters, and inducible promoters

(para 26). It is also noted that Savakis et al also contemplates that the sequence of the transposase may be modified to optimize codon usage and thus, increase transposition frequencies. It is noted that Savakis et al describe that optimization of codon usage by converting less frequently used codons to more frequently used codons is a method well known in the art to increase the expression levels of a given gene (see para. 143). **Loukeris** teaches that efforts to transfer the Drosophila germ-line transformation into Diptera of economic and medical interest are unsuccessful because P elements from Drosophila melanogaster don't work in Drosophila Hawaiensis. Loukeris teaches one approach is to use P elements from distant species to Drosophila. As such, Savakis taken with Loukeris provide sufficient motivation to optimize the codon sequences of the Heinrich system.

Accordingly, in view of the teachings of Savakis taken with Loukeris codon optimization sequence

in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise gene of interest in operable linkage with a promoter. Prior to instant invention, it was generally known in the art that initiation codon of a prokaryotic gene such as one disclosed by Heinrich would not be functional in Diptera species system unless it is modified to include a codon optimization.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Claims **1, 17, 25-27** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Bessereau et al., 2000 (WO**

00/073510 A1); **Savakis et al (EP0955364 A2); Horn et al** (Nature Biotechnology, 21: 64-70, 2003 (IDS).

The teachings of Heinrich applied here as indicated above.

Heinrich does not teach developmental stage specific.

However, at the time of the instant invention Bessereau teaches transposon-mediated mutagenesis in a C. elegans genome by introducing a transgene construct comprising a transposase gene under the control of an inducible promoter heat-shock promoter or a tetracycline-regulated promoter, into the C. elegans genome and the expressed transposase cause a transposon in the C. elegans to transpose and cause a mutation, wherein the transposon can be endogenous or heterologous transposon, such as Drosophila mariner element (e.g. abstract, p. 4 lines 18-22, claims 20-27, p. 12 lines 17-29). Bessereau only teaches using plasmid DNA for mutagenesis but does not teach using viral vector for the introduction of the transposon or DNA sequence encoding transposase into the C. elegans genome. Savakis supplements the teachings of Bessereau by teaching inducing mutation in a cell or producing a transgenic animal and progeny thereof by introducing an isolated transposable element, such as Minos, and a nucleic acid sequence encoding a transposase protein into a germ line cell, for example embryonic stem cell, of an animal, wherein the transposable element and the nucleic acid sequence encoding the transposase protein are incorporated into a viral vector (e.g. claim 1, 12, [0075], p. 12). Suitable promoters for the expression of a protein encoded by the nucleic acid sequence include heat shock promoters (e.g. [0026] to [0031]). Nucleic acid sequence of interest can be introduced into a mammalian cell using the Minos transposable elements and the modified Minos transposable element containing the nucleic acid of interest can be in a viral vector, and the DNA sequence encoding a transposase protein can be inserted into a viral vector. The viral vectors include retrovirus,

adenovirus, parvovirus (adeno-associated virus), and negative strand RNA virus etc. (e.g. [0047], [0049]). **Horn et al** (Nature Biotechnology, 21: 64-70, 2003) supplements the teachings of Bessereau/Savakis by teachings a transgene-based dominant embryonic lethality system that allows for generation of large quantities of competitive but sterile insects which system involves the ectopic expression of a hyperactive pro-apoptotic hid gene that causes embryo lethality when driven by the tetracycline-controlled transactivator (tTA) under the regulation of a cellularization gene enhancer-promoter in Drosophila melanogaster (abstract). Horn teaches the embryonic lethality can be suppressed maternally, which will allow it to be combined with transgenic female-specific lethality systems to raise only vigorous but sterile males (abstract).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the viral vector comprising the transposon and/or the DNA sequence encoding the tranposase to generate mutations in C. elegans because Savakis teaches introducing a viral vector comprising the Minos transposon and/or the DNA sequence encoding a transposase into a cell to induce mutation in said cell or to produce a transgenic animal, One of ordinary of skill in the art would have been particularly motivated since Horn suggested the embryonic lethality can be suppressed maternally, which will allow it to be combined with transgenic female-specific lethality systems to raise only vigorous but sterile males and the male sterility system should be suitable for initial stability tests or mass rearing in transgenic based SIT programs(p 69, 1st column). One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to generate mutations in C. elegans genome as taught by Bessereau with reasonable expectation of success.

Claims **33-35** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Heinrich et al** [PNAS, 97(15): 8229-8232, 2000 (IDS)] in view of **Horn et al** (Nature Biotechnology, 21: 64-70, 2003 (IDS)) and further in view of **Horn et al** (Dev Genes Evol, 210:623–629, 2000).

The teachings of Heinrich and Horn et al (Nature Biotechnology, 21: 64-70, 2003) are applied here as indicated above.

Heinrich taken with Horn et al (Nature Biotechnology, 21: 64-70, 2003) do not teach an expression marker to said system.

However, at the time of the time of the instant invention Horn et al (Dev Genes Evol, 210:623–629, 2000) teaches a highly sensitive, fluorescent transformation marker for Drosophila transgenesis (title). One having ordinary skill in the art at the time the invention was made would have been motivated to use said marker in order to select transgenic organisms at different stages of development as taught by Horn et al (Dev Genes Evol, 210:623–629, 2000) with reasonable expectation of success.

Thus, the claimed invention as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene k. Sgagias whose telephone number is (571)272-3305. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

(PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anne-Marie Falk/
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